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Brief Report

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A Method to Improve Continuous Renal Replacement Therapy Circuit Survival Time in Critically Ill Coronavirus Disease 2019 Patients With Acute Kidney Injury

Meint Volbeda, MD[1]; Mark Londema, MD[1]; Matijs van Meurs, MD, PhD[1]; Coen A. Stegeman, MD, PhD[2]; Ron T. Gansevoort, MD, PhD[2]; Stefan P. Berger, MD, PhD[2]; Peter H. J. van der Voort, MD, PhD[1]; Casper F. M. Franssen, MD, PhD[2]

Objectives: Optimizing continuous renal replacement therapy circuit survival in coronavirus disease 2019 patients admitted to the ICU.

Design: Single-center prospective observational cohort study.

Setting: Tertiary academic teaching ICU.

Patients: Between March 19, 2020, and May 18, 2020, 11 out of 101 coronavirus disease 2019 patients were treated with continuous renal replacement therapy comprising 127 continuous renal replacement therapy days.

Interventions: A nonrandomized observational comparison of circuit anticoagulation modalities using standard regional citrate anticoagulation, continuous IV heparin anticoagulation, or the combination of regional citrate anticoagulation with either continuous IV heparin or therapeutic dose nadroparin.

Measurements and Main Results: Circuit patency was shorter than 24 hours using standard regional citrate anticoagulation or continuous IV heparin anticoagulation. Median circuit survival increased with at least 165% when the combination of regional citrate anticoagulation with either continuous IV heparin or therapeutic dose nadroparin was applied.

Conclusions: Continuous renal replacement therapy circuit patency is diminished in coronavirus disease 2019 ICU patients. Combining regional citrate anticoagulation with either continuous IV heparin or therapeutic dose nadroparin increases filter survival as compared with regional citrate anticoagulation alone in this nonrandomized observational study.

Key Words: acute kidney injury; anticoagulation; continuous renal replacement therapy; coronavirus disease 2019; critically ill

The spread of the 2019 novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) throughout the world is a massive challenge for critical care facilities worldwide. While severe hypoxic respiratory failure is a key feature, a substantial proportion of patients with coronavirus disease 2019 (COVID-19) on the ICU also need renal replacement therapy (RRT) with reported incidences ranging from 5.6% to 61% (1). We initially observed remarkably short filter survival times due to frequent clotting of the extracorporeal circuit in the first patient with COVID-19 on continuous RRT (CRRT) in our center in March 2020. At that time, we received similar observations from colleagues in Italy, Spain, and the Netherlands. In a French multicenter prospective ICU study on thrombosis risk in patients with COVID-19, a shorter median lifespan of the CRRT circuit was observed in 28 of 29 patients (96.6%) and the total number of used CRRT circuits per patient was higher in COVID-19 patients (2). Achieving adequate CRRT circuit survival times is highly relevant to avoid shortages in disposables (3, 4). Here we describe our experiences with CRRT in the first cohort of patients with COVID-19 in our ICU, and we compare filter survival using different methods of circuit anticoagulation.

MATERIALS AND METHODS

All consecutive COVID-19 patients during the first Netherlands COVID-19 peak, who were admitted to the ICU of our tertiary care academic teaching hospital between March 19, 2020, and May 18, 2020, were included in this descriptive study. The local Medical Ethics Review Board reviewed and waived (M20.252810) this study. All patients received increased thrombosis prophylaxis with subcutaneous nadroparin 5,700 international units (IUs) once daily, or a therapeutic dose when indicated.

CRRT was performed using Prismaflex (Baxter, Lund, Sweden) and Prismax (Baxter, Brooklyn Park, MN) systems with Prismaflex

[1]Department of Critical Care, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

[2]Department of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

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ST 150 filterset (Baxter, Meyzieu Cedex, France) with a blood flow of 170–210 mL/min and an ultrafiltration rate of 30–47 mL/kg/hr. Venous access was obtained with a double-lumen 13F central venous catheter (high-flow double-lumen catheter; Baxter, Hechingen, Germany). Prior to being connected to the patient, the CRRT circuit was primed with 10.000 IU heparin (Leo Pharma BV, Amsterdam, The Netherlands). Regional citrate anticoagulation (RCA) was used as the first line anticoagulation modality, according to the Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Acute Kidney Injury (AKI) (5), with a citrate concentration of 2.2 mmol/L. When no coagulation occurred, the CRRT circuit was replaced after reaching a lifespan of 72 hours. In patients who were already treated with therapeutic subcutaneous doses of nadroparin, nadroparin treatment was continued during CRRT with RCA. If filter lifespan was shorter than 24 hours in patients who were not treated with therapeutic doses of nadroparin, a switch was made from RCA to continuous IV heparin administration at the arterial side of the circuit with a target activated partial thromboplastin time (APTT) of less than 45 seconds. When persistent short circuit survival times were observed with this anticoagulation protocol, a target APTT of 45–55 seconds was applied in subsequent CRRT sessions. When filter lifespan remained less than 24 hours, we combined RCA with continuous IV heparin administration.

Filter lifespans with different types of anticoagulation are given as a median with interquartile range (IQR) and were compared with Mann-Whitney *U* test. The same test was used for the comparison of the filter lifespan between patients with COVID-19 and a recent cohort of 20 non-COVID-19 patients.

RESULTS

A total of 101 patients with COVID-19 were treated in our ICU, of whom 11 patients required CRRT for a total of 127 CRRT days. Patient characteristics are shown in **Table S1** (http://links.lww.com/CCX/A384).

Standard RCA and continuous IV heparin anticoagulation were applied in eight and 12 circuits, respectively. Combined RCA with continuous heparin or therapeutic nadroparin administration was used in 46 and 24 circuits, respectively.

Anticoagulation with RCA or continuous IV heparin alone resulted in a median circuit patency of 10.7 hours (IQR, 5.6–16.3 hr) and 11.4 hours (IQR, 7.5–14.0 hr), respectively (**Fig. 1**). In contrast, the median circuit survival times in our center in 20 recent non-COVID-19 ICU patients treated with CRRT with RCA or continuous IV heparin were 37.8 hours (IQR, 22.1–64.8 hr; $p < 0.0001$ compared with COVID-19 patients) and 66.5 hours (IQR, 27.4–71.1 hr; $p < 0.0001$ compared with COVID-19 patients), respectively.

The combination of RCA with either continuous IV heparin or therapeutic nadroparin administration resulted in longer median circuit survival times of 27.2 hours (IQR, 16.7–61.3 hr) and 18.75 hours (IQR, 8.7–35.1 hr), respectively (compared to RCA alone $p = 0.0007$ and $p = 0.072$, respectively). Between patients that were treated with the combination of RCA and continuous IV heparin, there was no difference in filter survival time during APTT less than 45 seconds (median 34.3 hr, IQR 18.8–72.4) versus an APTT range of 45–55 seconds (median 27.2 hr, IQR 16.4–59.6) ($p = 0.47$). Filter survival during circuit anticoagulation with continuous IV heparin alone did also not increase with the application of a higher APTT range of 45–55 seconds (median 11.5 hr, IQR 8.3–13.2) versus an APTT less than 45 seconds (7.5 hr, IQR 3.3–16.8) ($p = 0.56$).

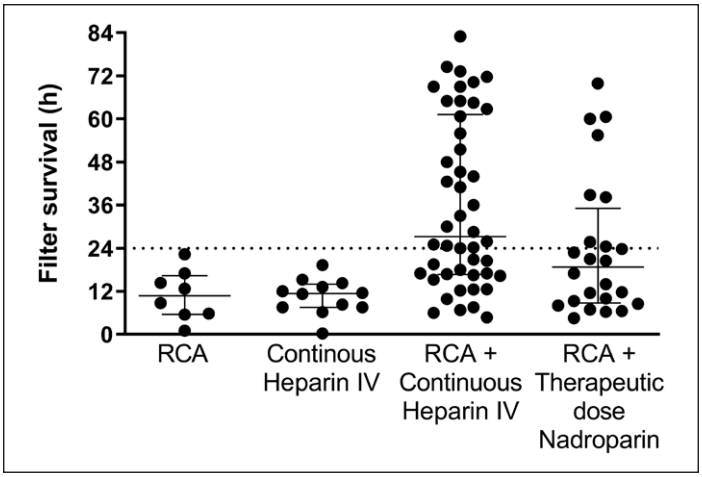

Figure 1. Filter survival. Median circuit patency's. *Error bars* indicate median and interquartile. RCA = regional citrate anticoagulation.

Bleeding complications were observed in two out of 11 patients during combined treatment with RCA and heparin, both with a target APTT range of 45–55 seconds. One patient suffered from bleeding lesions in the gastric cardia, and one patient suffered from intracerebral hemorrhage in the pons and thalamus which might be due to an episode of severe hypertension prior to the start of CRRT.

DISCUSSION

The major finding of this observational cohort study was that CRRT circuit patency in all ICU patients with COVID-19 was shorter than 24 hours using either standard RCA or continuous heparin treatment. Combining RCA with continuous heparin or therapeutic nadroparin administration increased the median circuit survival with at least 165%. A higher target APTT range during heparin treatment with or without RCA did not result in a longer filter lifespan as compared with a target APTT of less than 45 seconds.

Recent data suggest that ICU patients with COVID-19 have an increased risk of thromboembolic events (2). This COVID-19 associated coagulopathy is characterized by increased levels of fibrinogen and D-dimer (6) and may contribute to the decreased CRRT circuit survival times (2).

Our clinical observations suggest that RCA and heparin treatment alone are insufficient to prevent coagulation in the CRRT circuit in COVID-19 patients. However, since the number of CRRT circuits per anticoagulation modality in this report is limited, we still advise standard RCA as the initial anticoagulation modality. In case circuit survival is shorter than 24 hours, we suggest to combine RCA with continuous IV heparin administration.

Because of a potentially increased risk of bleeding and lack of longer circuit survival times at higher APTT target ranges, we suggest to use a target APTT less than 45 seconds when using heparin (7). In patients who have an indication for therapeutic low-molecular-weight heparin treatment, we suggest to combine this systemic anticoagulation treatment with RCA. In case of contraindications for RCA, we propose to start continuous replacement therapy with heparin anticoagulation and, when circuit survival is shorter than 24 hours, switch to intermittent hemodialysis since most patients with COVID-19 in the ICU are hemodynamically stable.

Our report has several limitations. First, we included the whole first COVID-19 wave in our observational study, but still have a relatively low number of patients. Second, as we describe our clinical process to optimize filter survival in AKI COVID-19 patients, our study had a nonrandomized, nonblinded observational character. Third, we analyzed a low number of covariates. Despite these limitations, our study is the largest series of patients with COVID-19 with detailed description of circuit survival time comparing different modes of anticoagulation. Thus, we chose to share our experiences already in this early stage in order to contribute to optimization of CRRT treatment in patients with COVID-19 including the prevention of shortages in CRRT filtersets in ICUs confronted with the 2019 novel coronavirus SARS-CoV-2. Future larger randomized trials should study the best anticoagulation regimen for CRRT in critically ill COVID-19 patients with AKI.

CONCLUSIONS

CRRT circuit patency is diminished in COVID-19 ICU patients. The combination of RCA with either continuous IV heparin or therapeutic dose nadroparin increased filter survival as compared with RCA alone. The efficacy and safety of these anticoagulation regimens should be confirmed in larger studies.

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For information regarding this article, E-mail: m.volbeda@umcg.nl

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